

CLAIMS

1. A compound having the formula A-(LM)-C, wherein A comprises a TF antagonist; LM comprises an optional linker moiety; and C comprises a cytotoxic domain.
2. The compound according to claim 1, wherein the TF antagonist is an inactive FVIIa polypeptide.
3. The compound according to claim 2, wherein the inactive FVIIa polypeptide is native human FVIIa or a fragment thereof catalytically inactivated in the active site.
4. The compound according to claim 3, wherein the inactive FVIIa polypeptide is native human FVIIa catalytically inactivated in the active site.
5. The compound according to claim 2, wherein C or (LM)-C is conjugated to the active site of the FVIIa polypeptide.
6. The compound according to claim 2, wherein the FVIIa polypeptide is catalytically inactivated in the active site with a chloromethyl ketone inhibitor independently selected from the group consisting of Phe-Phe-Arg chloromethyl ketone, Phe-Phe-Arg chloromethylketone, D-Phe-Phe-Arg chloromethyl ketone, D-Phe-Phe-Arg chloromethylketone Phe-Pro-Arg chloromethylketone, D-Phe-Pro-Arg chloromethylketone, Phe-Pro-Arg chloromethylketone, D-Phe-Pro-Arg chloromethylketone, L-Glu-Gly-Arg chloromethylketone and D-Glu-Gly-Arg chloromethylketone, Dansyl-Phe-Phe-Arg chloromethyl ketone, Dansyl-Phe-Phe-Arg chloromethylketone, Dansyl-D-Phe-Phe-Arg chloromethyl ketone, Dansyl-D-Phe-Phe-Arg chloromethylketone, Dansyl-Phe-Pro-Arg chloromethylketone, Dansyl-D-Phe-Pro-Arg chloromethylketone, Dansyl-Phe-Pro-Arg chloromethylketone, Dansyl-D-Phe-Pro-Arg chloromethylketone, Dansyl-L-Glu-Gly-Arg chloromethylketone, and Dansyl-D-Glu-Gly-Arg chloromethylketone.
7. The compound according to claim 2, wherein LM comprises a chloromethyl ketone inhibitor independently selected from the group consisting of Phe-Phe-Arg chloromethyl ketone, Phe-Phe-Arg chloromethylketone, D-Phe-Phe-Arg chloromethyl ketone, D-Phe-Phe-Arg chloromethylketone Phe-Pro-Arg chloromethylketone, D-Phe-Pro-Arg chloromethylketone, Phe-Pro-Arg chloromethylketone, D-Phe-Pro-Arg chloromethylketone, L-Glu-Gly-Arg chloromethylketone.

methylketone and D-Glu-Gly-Arg chloromethylketone, Dansyl-Phe-Phe-Arg chloromethyl ketone, Dansyl-Phe-Phe-Arg chloromethylketone, Dansyl-D-Phe-Phe-Arg chloromethyl ketone, Dansyl-D-Phe-Phe-Arg chloromethylketone, Dansyl-Phe-Pro-Arg chloromethylketone, Dansyl-D-Phe-Pro-Arg chloromethylketone, Dansyl-Phe-Pro-Arg chloromethylketone, Dansyl-L-Glu-Gly-Arg chloromethylketone, and Dansyl-D-Glu-Gly-Arg chloromethylketone, wherein the inactive FVIIa polypeptide is catalytically inactivated in the active site with said chloromethyl ketone inhibitor.

8. The compound according to claim 1, wherein the TF antagonist is an antibody against TF.
9. The compound according to claim 8, wherein the antibody is a human monoclonal antibody against human TF.
10. The compound according to claim 1, wherein C is selected from the group consisting of: protein ionophores, cytostatic agents, chemotherapeutic compounds, compounds which induce apoptosis, compounds containing radionuclides, and antisense nucleotide molecules independent selected from the group consisting of PNAs, DNAs, RNAs and LNAs.
11. The compound according to claim 1, wherein C comprises a cytotoxic protein or peptide.
12. The compound according to claim 11, wherein C comprises the amino acid sequence (KLAKLAK)_n, wherein n is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8.
13. The compound according to claim 12, wherein C has the amino acid sequence (KLAK-LAK)₂.
14. The compound according to claim 1, wherein C or (LM)-C is conjugated to an oligosaccharide side chain present on A.
15. The compound according to claim 1, wherein C or (LM)-C is conjugated to a free sulphhydryl group present on A.
16. The compound according to claim 1, wherein the compound comprises more than one binding site for TF.

17. The compound according to claim 1, wherein LM comprises an amino acid sequence.
18. The compound according to claim 17, wherein LM comprises the amino acid sequence Gly-Gly.
19. The compound according to claim 1; wherein LM comprises a molecule selected from the group consisting of: straight or branched C₁₋₅₀-alkyl, straight or branched C₂₋₅₀-alkenyl, straight or branched C₂₋₅₀-alkynyl, a 1 to 50 -membered straight or branched chain comprising carbon and at least one N, O or S atom in the chain, C₃₋₈cycloalkyl, a 3 to 8 -membered cyclic ring comprising carbon and at least one N, O or S atom in the ring, aryl, heteroaryl, amino acid, the structures optionally substituted with one or more of the following groups: H, hydroxy, phenyl, phenoxy, benzyl, thienyl, oxo, amino, C₁₋₄-alkyl, -CONH₂ , -CSNH₂, C₁₋₄ monoalkylamino, C₁₋₄ dialkylamino, acylamino, sulfonyl, carboxy, carboxamido , halogeno, C₁₋₆ alkoxy, C₁₋₆ alkylthio, trifluoroalkoxy, alkoxy carbonyl, haloalkyl.
20. The compound according to claim 1, wherein LM comprises a chemical bond that can be broken by chemical reduction.
21. The compound according to claim 20, wherein LM comprises a disulfide bond.
22. The compound according to claim 21, wherein the disulfide bond is between two cysteines.
23. The compound according to claim 1, wherein LM comprises a cleavage site for enzymatic hydrolysis by a protease.
24. The compound according to claim 23, wherein the protease is selected from the group consisting of cathepsin B, cathepsin D, cathepsin E, cathepsin G, cathepsin H, cathepsin L, cathepsin N, cathepsin S, cathepsin T, cathepsin K, and legumain.
25. The compound according to claim 24, wherein the protease is cathepsin B.
26. The compound according to claim 23, wherein LM comprises the amino acid sequence Phe-Arg.

27. A pharmaceutical composition comprising (i) an amount of the compound having the formula A-(LM)-C, wherein A comprises a TF antagonist; LM comprises an optional linker moiety; and C comprises a cytotoxic domain; and (ii) a pharmaceutically acceptable carrier or excipient.
28. A compound for use as a medicament having the formula A-(LM)-C, wherein A comprises a TF antagonist; LM comprises an optional linker moiety; and C comprises a cytotoxic domain; and wherein said compound binds to TF and inhibits TF function.
29. A method for preventing or treating disease or disorder associated with pathophysiological TF function, said method comprising contacting a TF presenting cell with a compound having the formula A-(LM)-C, wherein A is a TF antagonist; LM is an optional linker moiety; C comprises a cytotoxic domain.
30. The method according to claim 29, wherein the disease or disorder associated with pathophysiological TF function is selected from the group consisting of: deep venous thrombosis, arterial thrombosis, post surgical thrombosis, coronary artery bypass graft (CABG), percutaneous transdermal coronary angioplasty (PTCA), stroke, cancer, tumour metastasis, angiogenesis, ischemia/reperfusion, rheumatoid arthritis, thrombolysis, arteriosclerosis and restenosis following angioplasty, acute and chronic indications such as inflammation, septic shock, septicemia, hypotension, adult respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC), pulmonary embolism, platelet deposition, myocardial infarction, and the prophylactic treatment of mammals with atherosclerotic vessels at risk for thrombosis.
31. A method for preventing or treating disease or disorder associated with pathophysiological TF function in a mammal in need of such treatment, said method comprising administering to said mammal a therapeutically effective amount of at least one compound as defined in claim 1 in combination with a pharmaceutical acceptable excipient and/ or carrier.